The Basal Ganglia and Beat Perception in Parkinson's Disease

by

Sariha Ima Moyen

A Thesis Submitted in Partial Fulfillment of the

Requirements for the Degree of Bachelor of Science

With Honors in Biopsychology, Cognition, and Neuroscience from the

University of Michigan

2012

Advisors: Dr. Rachael D. Seidler

Dr. Nathaniel S. Miller

Abstract

Parkinson's disease (PD) is characterized by dopaminergic cell loss in the basal ganglia (BG) that causes motor impairments of speech and gait. These symptoms may result from difficulty generating an internal beat (Freeman, Cody, Schady, 1993; Jahanshahi et al., 1995), with the BG serving as an "internal clock." I investigated this by administering a diagnostic task of listening strategy to young adults, older adults, and PD patients. No significant differences were found between age/disease groups, in terms of the listening strategy recruited by participants. However, trends approaching significance suggested PD patients taking dopamine agonists showed less accuracy on the timing task when compared to subjects taking levodopa-carbidopa, and older-onset PD patients had less accuracy relative to young-onset PD patients. These findings suggest the BG may not play a strong role in beat perception; however, individual differences in PD symptoms and clinical factors, such as medications and age of disease onset, may modulate timing processes.

Keywords: Parkinson's disease, basal ganglia, beat perception

The Basal Ganglia and Beat Perception in Parkinson's Disease

Background on Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, currently affecting approximately 10 million people worldwide (de Lau & Breteler, 2006; Morris, 2000). PD typically affects older adults (65-90 years of age), but young-onset PD can occur as early as 30-40 years of age (Lang & Lozano, 1998a; Morris, 2000). PD is primarily characterized by motor symptoms, such as tremor, rigidity, difficulty starting movement (akinesia), slowness of movement (bradykinesia), postural instability, gait impairments, and monotonous, soft speech with a variable rate (dysarthia; Jankovic, 2007; Lang & Lozano, 1998a). Likewise, perceptual and cognitive impairments, such as loss of smell and memory impairments, are common in PD (Davis, 2008; Forno, 1996; Meireles & Massano, 2012).

The motor symptoms of PD are primarily due to dopaminergic denervation (cell loss) in the basal ganglia (BG; Forno, 1996; Lang & Lozano, 1998a). Initially, the dopaminergic cell loss is concentrated within the nigrostriatal pathway, but as the disease progresses, the cell loss spreads to cortical regions (Bear, Connors, Paradiso, 2007; Jones & Jahanshahi, 2009). This dopamine deficiency results in an imbalance of the excitatory and inhibitory pathways in the BG, which ultimately leads to the disordered movement shown in PD (Lang & Lozano, 1998b). What triggers the dopamine loss is unknown (Bear et al., 2007; Lang & Lozano, 1998b).

Pharmacological Treatment for PD

The gold standard treatment of PD is levodopa-carbidopa, which is a dopamine precursor that directly replaces tonic dopamine levels in the brain, thus compensating for the loss of dopaminergic neurons in PD (Hornykiewicz, 1998). However, other medications, such as dopamine agonists or COMT inhibitors, may also be used to regulate dopamine levels within the

brain (Rascol et al., 2003). Dopamine agonists stimulate postsynaptic dopamine receptors, while COMT inhibitors slow down the metabolism of levodopa, thereby increasing the drug's half-life (Bonuccelli, Dotto, & Rascol, 2009; Rascol et al., 2003). While these medications are relatively effective for treating some motor symptoms of the disease, gait and speech symptoms of PD are relatively unresponsive to anti-parkinsonian medications (Rascol et al., 2003).

Temporal Processing Impairments in PD

One hypothesis for the speech and gait impairments is that PD patients have difficulty internally generating and maintaining a rhythm (Freeman et al., 1993; Jahanshahi et al., 1995). In accord with this hypothesis, both speech and gait impairments in PD show abrupt starts and stops that disrupt the regularity of these rhythmic movements (Harel, Cannizzaro, Cohen, Reilly, Snyder, 2004; Kegl, Cohen, Poizner, 1999; Nieuwboer et al., 2001). For example, Skodda and Schlegel (2008) found that PD patients had an increased speech rate, but paused less frequently and for a longer period of time, in comparison to age-matched controls. Similarly, PD patients may show freezing of gait while walking, where the legs, arms, and eyelids suddenly stop moving (Jankovic, 2007). However, studies have also shown that when PD patients speak or walk in synchrony with a metronome, the rhythmic impairments of speech and gait temporarily improve (Thaut et al., 1996; Thaut, McIntosh, McIntosh, Hoemburg, 2001).

To understand rhythm generation in PD, studies have investigated duration perception and production (temporal processing) in healthy older and young adults relative to PD patients, and provide evidence that PD patients have difficulty internally generating a beat (Elsinger et al., 2003; Grahn & Brett, 2009). However, the literature on temporal processing impairments in PD patients is rather mixed, with some studies reporting temporal processing deficits (Artieda, Pastor, Lacruz, & Obeso, 1992; Merchant, Luciana, Hooper, Majestic, Tuite, 2008; O'Boyle,

Freeman, & Cody, 1996; Pastor, Artieda, Jahanshahi, & Obeso, 1992) while others do not (Riesen & Schnider, 2001; Spencer & Ivry, 2005).

The mixed literature on temporal processing impairments in PD patients may be attributed to individual, or subgroup, differences. Providing some support for this hypothesis, Merchant et al. (2008) found two types of PD patients; individuals with higher timing variability on the timing perception and production task, and individuals with lower timing variability when compared to age-matched controls. Additionally, PD patients are heterogeneous in the presentation of PD symptoms, along with other clinical factors, such as age of diagnosis and types of PD medications used for treatment (Jankovic et al., 1990; Lewis et al., 2005; Zetusky, Jankovic, Pirazzolo, 1985). The heterogeneity of PD patients, along with the mixed literature on impaired duration perception and production in PD, highlights the need to consider individual differences in temporal processing.

Brain Regions Involved in Temporal Processing

Animal, pharmacological, neuropsychological, and brain imaging studies have provided converging evidence for the involvement of a network of brain regions in temporal processing, including the cerebellum, prefrontal cortex, BG, supplementary motor area (SMA), and the pre-supplementary motor area (Coull, Cheng, & Meck, 2011; Jones and Jahanshahi, 2009; Macar et al., 2002; Meck, 1996; Wiener, Turkeltaub, & Coslett, 2010). The cerebellum and BG are thought to play a major role in temporal processing; however the specific roles of these regions are unclear. Specifically, the BG are posited to serve as the "internal clock" (Coull et al., 2011; Grondin, 2010; Jones & Jahanshahi, 2009; Meck, 1996). Evidence for this is shown in experiments with lesions to the substantia nigra pars compacta or other striatal lesions in rats, resulting in timing impairments (Meck 2006). Brain imaging studies in humans have also shown

activation of the BG in a variety of duration perception and production tasks (Coull, Nazarian, & Vidal, 2008; Harrington et al., 2004; Pouthas et al., 2005) as well as activation in frontostriatal regions, including the SMA and prefrontal cortex (Coull et al., 2011; Macar et al., 2002). Grahn and colleagues (Grahn & Brett, 2007; Grahn & Brett, 2009; Grahn & McAuley, 2009) not only found that both the BG and SMA were activated when young adults heard rhythmic sequences, but that activation intensity differed by listening strategy, where strong beat perceivers had greater activation of the SMA when compared to weak beat perceivers.

Theories of Time Perception

Two broad theoretical perspectives have been proposed to explain the internal clock used for beat perception and production: an interval-based or a beat-based (entrainment) perspective (Grondin, 2010). The *interval-based* timing perspective takes an information processing approach to explain the internal clock, separating timing processes into three separate stages: clock, memory, and decision. From this perspective, the internal clock acts as a stopwatch that can be started, stopped, and reset arbitrarily. The internal clock emits pulses to match the duration of a time interval. These pulses are collected in the accumulator, stored in memory, and used later as a referent to judge the durations of future time intervals. Alternatively, the *beat-based* perspective views the clock as an endogenous oscillator that entrains (synchronizes) to temporal events in the environment and generates expectancies about the occurrence of future events in time.

In general, interval-based models tend to provide more accurate predictions when applied to timing of single durations, while beat-based models more accurately predict the timing of rhythmic sequences. For example, the interval-based strategy would be better when using baking knowledge from previous experiences to time how long it will take for a cake to finish

cooking. On the other hand, the beat-based strategy would work better when humming to a song, in order to keep up with the speed at a particular moment, since songs have continuous rhythmic sequences of time intervals. Historically, these two perspectives on the internal clock have been considered competing theories; however, recent work by McAuley and colleagues (Grahn & McAuley, 2009; McAuley, Frater, Janke, & Miller, 2006) suggests that individuals may recruit *either* an interval- or beat-based strategy when listening to an ambiguous rhythmic sequence. That is, individuals vary in their propensity to rely on one type of strategy versus the other.

Ambiguous Tempo Discrimination Task

McAuley and colleagues (Grahn & McAuley, 2009; McAuley et al., 2006) developed an ambiguous tempo discrimination task to investigate individual differences in the recruitment of interval- or beat-based listening strategies. For these experiments, participants heard both control and test tone sequences (Figure 1), in which the tempo (rate) of the sequence was marked by tone onsets, or the interonset intervals. The control sequence, which is commonly used in studies of temporal processing, consisted of a 600 ms time interval, followed by a 1200 ms time interval, and a variable final time interval centered on 600 ms. The test sequence, a modified version of the control sequence, consisted of two 300 ms time intervals, followed by a 1200 ms time interval, and a variable final time interval yoked to 600 ms. For both the control and test sequences, participants judged whether the final time interval of the sequence was "speeding up" or "slowing down." The test sequence was ambiguous since it allowed individuals to judge the speed of the sequence using either the explicit 300 ms referents (marked by the two pairs of tone intervals) or the implicit 600 ms referent.

More beat-based individuals used the implied 600 ms referent, and judged sequences as "speeding up" when the final time interval was less than 600 ms, and as "slowing down" when

the final time interval was greater than 600 ms. Hearing regular 600 ms time intervals throughout the test sequence is analogous to hearing a repetitive "beat," and is what deems this strategy as beat-based. Interval-based listeners mostly judged the sequences as "slowing down," suggesting the use of the initial 300 ms referents, as the final variable time interval would always be greater than 300 ms. In contrast to a beat-based strategy, the interval-based strategy either uses an explicitly isolated time interval or uses an average of adjacent time intervals to judge the end of the test sequence. Approximately 33% of the young adults were interval-based listeners, while 44% were beat-based listeners. The other participants did not fit into either category (McAuley et al., 2006).

Later work by Grahn and McAuley (2009) used functional magnetic resonance imaging (fMRI) to test whether different brain regions were recruited based on an individual's listening strategy. All participants showed activation of areas such as the basal ganglia, cerebellum, and the premotor cortex. However, strong beat perceivers had greater activation in the left SMA, left premotor cortex, and left insula, whereas weak beat perceivers had greater activation in the right premotor cortex and left posterior superior temporal gyrus. Furthermore, differences in brain activation were present when individuals completed both the control and test sequences, suggesting that general processing differences may underlie these listening strategies.

Current Study

In this study, I extend the approach used by McAuley and colleagues to investigate performance on the ambiguous tempo discrimination task in PD patients. PD is of specific interest as it is associated with dopaminergic denervation of the BG and several theories posit a critical role of the BG and dopamine in beat perception and production (Coull et al., 2011; Grondin, 2010; Jones & Jahanshahi, 2009; Meck, 1996; Wiener et al., 2010). Previous studies

have shown that damage to the BG may relate to difficulties in temporal discrimination tasks where a beat is readily discernible (Grahn & Brett, 2007; Schwartze, Keller, Patel, & Kotz, 2011). In addition, recent fMRI studies using the ambiguous tempo discrimination task report differences in brain network activation between interval- and beat-based listeners in healthy individuals, yet both groups of listeners have shown activation of the BG (Grahn & McAuley, 2009).

In this thesis, I investigated the role of the BG in beat perception further by looking at individual differences in beat perception in PD patients. I hypothesized that PD patients would show weaker beat perception when compared to both young and older adults, due to dopaminergic denervation within the BG. If the BG plays a critical role in beat perception, PD patients will tend to show a more interval-based listening pattern, which would translate to weaker beat perception, when performing the ambiguous tempo discrimination task. To test this hypothesis, I administered the ambiguous tempo discrimination task to PD patients. I used a simple contrast model developed by Grahn and McAuley (2009) to quantify whether individuals recruited an interval- or beat-based listening strategy, called the *w* value. The *w* value is derived from an individual's proportion of "speeding up" responses for the test sequence, with values near 0 suggesting the use of an interval-based listening strategy, and values near 1 suggesting the use of a beat-based listening strategy. Since I predict PD patients to employ an interval-based strategy, I expect their proportion of "speeding up" responses as a function of the final time interval to show flatter psychometric curves, relative to older and young adult controls. Furthermore, I predict PD patients to have lower *w* values, in comparison to older and young adult controls, which would suggest a more interval-based listening strategy. Support for this hypothesis would provide further evidence for the role of the BG in beat perception.

Additionally, clarifying the role of the BG in PD patients could help track the progression of the disease or have translational implications for speech and gait rehabilitation in PD.

Method

Participants

Twenty-seven volunteers (8 female) with mild-to-moderate (Hoehn and Yahr Stage I–III; Hoehn & Yahr, 1967) idiopathic PD participated in return for monetary compensation. PD patients ranged in age from 40 – 83 years *(M* = 64.95, *SD* = 9.04) and had an average of 6.25 years of formal musical training (*SD* = 11.67). The average number of years post-PD diagnosis was 7.14 (*SD* = 3.94). All participants were taking anti-parkinsonian medications, such as levodopa-carbidopa and/or dopamine agonists, to treat their PD symptoms, and were tested while ON their regular medication(s). A trained rater administered the Unified Parkinson's Disease Rating Scale (Section III-Motor) to assess motor severity (Fahn, Elton, & UPDRS Committee, 1987). Table 1 provides additional patient characteristics. Patients' data were excluded from analysis if they were diagnosed with any neurological or psychiatric disease other than PD, or if they scored below 123 (maximum raw score = 144) on the Dementia Rating Scale (DRS-2; Jurica, Leitten, & Mattis, 2001), which is suggestive of greater than mild cognitive impairment. PD patients were recruited through support groups and movement disorder clinics in Northwestern Ohio and Southeastern Michigan. Seven patients were tested at Bowling Green State University, prior to thesis data collection.

Control participants were 23 older adult volunteers (19 female), ranging from 54 – 87 years of age, with an average age of 65.26 years (*SD* = 8.95) and 15 young adult volunteers (7 female), ranging in age from 18 – 29 years of age, with an average age of 22.79 years (*SD* = 3.7) with no known neurological or psychiatric disorder. Older adults had an average of 10.36 years

of musical experience (*SD* = 18.98), while young adults had an average of 2.26 years of experience (*SD* = 3.42). Tables 2 and 3 provide additional characteristics of the older and young adult participants. Collected data from older adult subjects were excluded from data analysis if they scored below a 123 on the DRS-2 (Jurica et al., 2001), or had any neurological or psychiatric disorders besides PD. All participants received monetary compensation for their participation in the study. Control participants were recruited and tested at Bowling Green State University as part of another research study.

All participants signed a consent form approved by the Institutional Review Board of Bowling Green State University or the University of Michigan.

Apparatus

Stimulus presentation and response collection were controlled with MIDILAB software (Todd, Boltz, & Jones, 1989) running on an IBM PC-compatible computer. The tone sequences were presented binaurally, at a comfortable listening level, through Sennheiser HD 280 Pro headphones controlled by a Rane HC 6 headphone console and attached to a Yamaha TX81Z FM tone generator. Participants responded by pressing one of two buttons on a MIDILAB response box.

Stimuli

Figure 1 shows a schematic of the two tone sequences participants heard during the study. The timing of the sequences was varied by changing the duration between tone onsets or the interonset interval. The control sequence consisted of four tones that marked an initial 600 ms time interval, followed by a 1200 ms time interval, and a variable final time interval centered on 600 ms. The test sequence was the same, except that it contained five tones; the additional tone in the test sequence subdivided the initial 600 ms time interval into two 300 ms time intervals.

The final time interval varied randomly from trial-to-trial and took on one of ten values yoked to the standard 600 ms time interval (384 ms, 432 ms, 480 ms, 528 ms, 576 ms, 624 ms, 672 ms, 720 ms, 768 ms, or 816 ms). This manipulation resulted in five of the control sequences objectively "speeding up" and five sequences "slowing down." Stimulus tones were 50 ms in duration with a fundamental frequency of 440 Hz.

Design

This experiment used a 2 (sequence: control, test) x 3 (age/disease group: young adult, older adult, PD patient) mixed measures design. Sequence was a within-subject variable and age/disease group was a between-subject variable.

Procedure

Prior to testing, the experimenter read instructions to the participants. The directions instructed participants to judge whether the end of each sequence was "speeding up" or "slowing down" and emphasized that there were no right or wrong answers, and that it was acceptable to judge all sequences as either "slowing down," "speeding up," or a combination of "speeding up" and "slowing down." Participants responded by pressing one of two buttons on a response box.

Participants completed a familiarization block to ensure they understood the task. The familiarization block consisted of eight trials; both test and control sequences were presented in a randomized order. Changes in the final interval were large (420 ms, 510 ms, 690 ms, and 780 ms), so that it was easy to judge whether the control sequence was "speeding up" or "slowing down."

Five test blocks were presented. Each test block contained 60 trials, in which control and test sequences were presented in a randomized order. The order of trial blocks was counterbalanced between participants. The final time interval of the sequence took on values of

384 ms, 432 ms, 480 ms, 528 ms, 576 ms, 624 ms, 672 ms, 720 ms, 768 ms, or 816 ms and varied randomly from trial-to-trial. In total, 15 observations were obtained for each level of sequence and final time interval, resulting in 300 total trials. Participants were given 4000 ms to respond to each sequence, and a 2500 ms intertrial interval followed participants' responses. Each test block lasted approximately 10 minutes and participants received a rest break after completion of every two test blocks.

PD patients also completed two questionnaires related to their experiences with PD, including their perceived effectiveness of their anti-parkinsonian medications, as this can vary from day-to-day in patients, along with overall medication effectiveness fluctuating as the disease progresses (Lang & Lozano, 1998b). I administered the Medication Effectiveness Scale at the beginning and end of the testing session to assess medication effectiveness and fluctuations during testing (Goberman, Elmer, Mackowiak, & Heaton, 2004). For these measures, participants self-rated several PD symptoms, on a scale of 1-7 (1 = extreme, 7 = none), as well as how well they felt their PD medications were working at the moment (1 = not at all, 7 = perfectly).

Data Analysis

The primary dependent variables were the proportion of "speeding up" responses and *w* value, which was used to determine whether individuals recruited an interval- or beat-based listening strategy. To calculate *w* values, the proportion of "speeding up" responses for the 10 final time intervals of the test sequence for each participant were fit to a simple temporal contrast model (see Grahn and McAuley (2009) for full details) that assessed the extent to which participants' temporal judgments about the test sequence were based on a 300 ms or 600 ms reference interval. In this model, binary judgments ("speeding up"/"slowing down") on a given

trial are assumed to be based on either a 300 ms or a 600 ms referent (P = 300 or 600, respectively). The 300 ms referent correlates to the explicit time interval marked by the first three tones of the test sequence, whereas the 600 ms referent corresponds to an implied beat in the test sequence. If individuals were more likely to use the 300 ms referent, it suggested a weak beat-based (interval) system, whereas using the implied 600 ms referent indicated a stronger beat-based system.

For each final time interval, T_i, a temporal contrast metric, and C_i, which measures the normalized difference between the final time interval and each referent (P) were calculated:

$$C_i = \frac{(T_i - P)}{P}$$

This temporal contrast model has been shown to provide a good index of the temporal information participants use to make duration judgments (McAuley & Jones, 2003). Because participants can use one of two possible referents, each T_i results in two values of C_i, labeled as C_{i300} and C_{i600} for the P = 300 ms and 600 ms referents, respectively. Consistent with standard signal detection assumptions, temporal contrast metric values were assumed to be normally distributed with a standard deviation, σ (Macmillan & Creelman, 1991), and C_i-values were z-transformed and merged using a simple weighted average:

$$z = (1 - w)z_{i300} + wz_{i600}$$

Finally, the combined z-score was used to predict the proportions of "speeding up" responses for each final time interval by using a cumulative normal distribution function:

$$\text{P('speeding up')} = 1 - \varphi(z)$$

To fit the data to the model, I allowed both $w \in [0, 1]$ and σ to vary, minimizing the RMSE between the observed and predicted proportion of "speeding up" responses.

Importantly, the *w* value indicated whether an individual recruited an interval- or beat-based listening strategy for the test sequence, based on whether their duration judgments relied upon the explicit 300 ms or the implicit 600 ms referent. *W* values ranged on a continuous scale from 0 to 1, with values closer to 0 suggesting the recruitment of an interval-based listening strategy and values closer to 1 suggesting a more beat-based listening strategy.

To classify participants as using either an interval- or beat-based listening strategy, I performed a median split on *w* values within each age/disease group.[1] Additionally, to analyze PD medication effects on beat perception, participants were classified into three categories: those taking only levodopa-carbidopa, levodopa-carbidopa and a dopamine agonist, or only taking dopamine agonist(s).

A total of four older adults, one young adult, and six PD patients were removed from the final analyses due to either failure to follow task instructions or inattention during the experiment; in all cases, just-noticeable difference (JND) thresholds could not be calculated or were greater than two standard deviations above the mean. Data analysis was performed on 14 young adults, 19 older adults, and 21 PD patients; I tested 14 PD patients for the thesis project.

All statistical analyses were performed using SPSS version 19 for windows (SPSS, 2010) using an alpha level of 0.05. In cases where the assumption of sphericity was violated, the F-statistic was evaluated for significance using the Greenhouse-Geisser adjusted degrees of freedom for all ANOVA analyses.

Results

Research has shown general duration discrimination impairments in PD patients, relative to age-matched controls, as well as between older and young adults (Artieda et al., 1992; Grahn & Brett, 2009; Merchant et al., 2008). I performed a preliminary analysis on JNDs for the

control sequence to assess potential differences in duration discrimination thresholds between the age/disease groups. JNDs for the age/disease groups were submitted to a one-way ANOVA for independent measures, and were found to differ between the age/disease groups, $F(2, 53) = 3.61$, $p = .03$. Post hoc Tukey HSD tests revealed that PD patients had significantly higher JNDs, or worse discrimination thresholds ($M = 17.62$, $SE = 6.68$) than young adults ($M = 12.51$, $SE = 2.09$), but patients' JNDs did not differ relative to older adult controls ($M = 16.71$, $SE = 6.30$), $p = .03$ and $p = .87$. Older adults also had higher JNDs when compared to young adults; this trended towards significance, $p = .10$. Due to differences in JNDs between the age/disease groups, JNDs were used as a covariate in our analyses.

In order to quantify whether individuals recruited more of an interval- or beat-based listening strategy, studies have looked at the proportion of "speeding up" responses. McAuley and colleagues (Grahn & McAuley, 2009; McAuley et al., 2006) found that, when looking at the proportion of "speeding up" responses as a function of the final time interval, young adults had different psychometric curves for the test sequence, depending on their listening strategy. Figure 2 shows the average proportion of "speeding up" responses as a function of the final time interval for both the control and test sequences for young adults, older adults, and PD patients. Most participants judged the control sequence as "speeding up" when the final time interval was greater than 600 ms, and "slowing down" when the final time interval was less than 600 ms, resulting in an S-shaped curve that is frequently observed for this type of sequence. Though participants in all three age/disease groups performed similarly, the psychometric curves tended to vary more around 552 ms to 696 ms in the control sequence (Figure 2a). Furthermore, both interval- and beat-based listeners from all three age/disease groups had S-shaped curves.

In contrast to the control sequence, participants across all three age/disease groups showed a split in responses for the test sequence based on their listening strategy. Beat-based listeners judged the sequence as "speeding up" when the final time interval was less than 600 ms, and "slowing down" when the final time interval was greater than 600 ms, showing a similar pattern of responses to the control sequence. However, interval-based listeners, on average, also judged the sequence as "speeding up" when the final time interval was less than 600 ms, but their curves flattened out into horizontal lines, meaning that many interval-based listeners judged the sequences as "slowing down" more often than participants who had recruited a beat-based strategy.

A 2 (sequence: control, test) x 2 (listening strategy: beat-based, interval-based) x 3 (age/disease group: young adult, older adult, PD patient) x 10 (final time interval: 384 ms, 432 ms, 480 ms, 528 ms, 576 ms, 624 ms, 672 ms, 720 ms, 768 ms, and 816 ms) mixed measures ANOVA on the proportion of "speeding up" responses was conducted to assess differences across age/disease groups in listening strategy. Based on my primary hypothesis, I predicted PD patients would show flatter or more curvilinear shaped lines relative to young and older adult controls, regardless of listening strategy, which would support my hypothesis of weaker beat perception in PD patients. Contrary to my hypothesis, the critical four-way interaction between sequence, listening strategy, age/disease group, and final time interval was not significant, $F(7.61, 178.93) = 0.24$, $p = .98$. Moreover, I did not find an effect of group, suggesting that young adults, older adults, and PD patients did not differ from each other on their proportions of "speeding up" responses for the control and test sequences, $F(2, 47) = 1.25$, $p = .30$.

The mixed measures ANOVA revealed several interactions, including a three-way interaction between sequence, final time interval, and listening strategy, listening strategy and

sequence, final time interval and listening strategy, and final time interval and sequence. The three-way interaction between sequence, final time interval, and listening strategy showed that listening strategy had a greater effect for the final time intervals in the test sequence, as beat-based listeners had significantly higher average "speeding up" responses relative to interval-based listeners, $F(3.81, 178.93) = 12.26$, $p < .001$. A two-way interaction between listening strategy and sequence revealed that beat-based listeners had higher average proportions of "speeding up" responses for the control ($M = 0.47$, $SE = 0.02$) and test ($M = 0.41$, $SE = 0.02$) sequences, when compared to interval-based listeners for the control ($M = 0.48$, $SE = 0.02$) and test sequences ($M = 0.17$, $SE = 0.02$), $F(1, 47) = 28.74$, $p < .001$. Another interaction between final time interval and listening strategy displayed that beat-based listeners also had higher mean proportions of "speeding up" responses across the 10 final time intervals compared to interval-based listeners, $F(3.99, 187.39) = 8.39$, $p < .001$. Additionally, an interaction between final time interval and sequence revealed that the mean proportions of "speeding up" responses were higher for the final time intervals in the control sequence relative to the test sequence, $F(3.81, 178.93) = 13.09$, $p < .001$.

Finally, I found several main effects including effects of sequence, final time interval, and listening strategy. The mean proportion of "speeding up" responses was higher for the control sequence ($M = 0.47$, $SD = 0.02$) relative to the test sequence ($M = 0.29$, $SD = 0.01$), $F(1, 47) = 14.93$, $p < .001$. Similarly, the mean proportion of "speeding up" responses was higher when the final time intervals were less than 600 ms, when compared to the mean proportion of "speeding up" responses for the final time intervals that were greater than 600 ms, $F(3.99, 187.39) = 132.03$, $p < .001$. The mean proportion of "speeding up" responses was also higher

when individuals were beat-based listeners (M = 0.44, SD = 0.01) when compared to interval-based listeners (M = 0.32, SD = 0.01), $F(1, 47) = 30.28$, $p < .001$.

The same analysis was performed on the proportion of "speeding up" responses, except that a median split on *w* values was created for all participants in the three age/disease groups, to assess individual differences in the listening strategy between groups. This analysis revealed the same pattern of results.

Another way to study differences in perception based on listening strategy is to look at the *w* value. To assess the effects of sequence-type between age/disease groups, I performed a 2 (sequence: control, test) x 3 (age/disease group: young adult, older adult, PD patient) mixed measures ANOVA on *w* values. Figure 3 shows the average *w* values as a function of age/disease group and sequence. For both control and test sequences, all three age/disease groups had similar *w* values. Based on my hypothesis that PD patients would be less likely to use a beat-based listening strategy, I predicted PD patients to have lower *w* values relative to older and young adult controls, for the test sequence. However, I did not find support for this hypothesis. No significant interactions nor main effects were found (ps > .14).

Few studies have looked at individual differences in *w* values, rather than looking at group averages (Grahn & McAuley, 2009; Snyder, Pasinski, & McAuley, 2011). Figure 4 shows each participants' *w* values as a function of age/disease group on the test sequence. Older adults and PD patients show greater dispersal in *w* values when compared to young adults, though, all three age/disease groups show a clustering toward *w* values closer to 1, suggesting that the group means in *w* values are fairly representative of the data.

A number of metrics also exhibited widely varying scores within the PD patient group, including musical experience, age of diagnosis, and anti-parkinsonian medications that

participants were taking during the testing session. I performed several follow-up analyses to assess whether these factors affected engagement of either an interval- or beat-based listening strategy.

Previous studies have considered whether years of musical experience affect beat perception strength and found no correlation between the two (Grahn, Henry, & McAuley, 2011; Grahn & McAuley, 2009). Years of musical experience included total number of years in dance, voice, and instrumental training. I conducted a bivariate Pearson correlation on all participants and also found no significant correlation between years of musical experience and *w* values, $r(19) = -0.28$, $p = .22$. Similarly, the total number of hours spent listening to music was not significantly correlated to *w* values, $r(19) = -0.27$, $p = .24$. On the other hand, a chi-square analysis revealed that there were differences in the distribution of gender among the age/disease groups, $x^2(2, 55) = 14.603$, $p < .001$. The PD patients included in the final data analysis consisted of more males ($n = 16$) than females ($n = 5$), while in the older adult control group there were more females ($n = 16$) than males ($n = 3$).

A recent study by Diederich, Moore, Leurgans, Chmura, & Goetz (2003) found that PD patients with older age of disease onset have greater motor impairment when compared to younger-onset PD patients. To address whether age of PD onset affected beat perception, I split the PD patients by those who were diagnosed before or at age 60 and those diagnosed at age 61 or older. I conducted a 2 (sequence: control, test) x 2 (age of diagnosis: under 60, 61 and older) x 2 (listening strategy: interval-based, beat-based) x 10 (final time interval: 384 ms, 432 ms, 480 ms, 528 ms, 576 ms, 624 ms, 672 ms, 720 ms, 768 ms, and 816 ms) mixed measures ANOVA on the proportion of "speeding up" responses to analyze the effect of age of diagnosis. Sequence and final time interval were within-subject factors, while age of diagnosis and listening strategy

were the between-subject factors. The split around age 60 was created because I had a smaller sample size of patients with a smaller age of disease onset range, and this grouping was similar to the split used by Diederich et al. (2003).

No significant four-way interaction was found between sequence, age of diagnosis, listening strategy, and final time interval, $F(3.87, 61.98) = 1.42$, $p = .24$. Moreover, no effect was found for age of diagnosis, suggesting that proportion of "speeding up" responses did not differ between patients diagnosed before or at 60 years of age when compared to patients diagnosed at age 61 years or older, $F(1, 16) = 2.58$, $p = .13$. However, a trending interaction between sequence, listening strategy, and age of diagnosis was found where people diagnosed with PD at or under the age of 60, who used a beat-based listening strategy, had higher mean proportion of "speeding up" responses ($M = 0.50$, $SE = 0.04$) on the test sequence, relative to patients with older age of disease onset ($M = 0.36$, $SE = 0.04$), $F(1, 16) = 3.24$, $p = .09$. There was another trend towards a two-way interaction between listening strategy and age of diagnosis, where young-onset PD patients who recruited a beat-based listening strategy had overall higher mean proportion of "speeding up" responses relative to other young- and older-onset PD patients using other listening strategies, $F(1, 16) = 2.82$, $p = .11$. Here, patients with young-onset PD, who used a beat-based listening strategy, had a higher mean proportion of "speeding up" responses ($M = 0.49$, $SE = 0.03$) when compared to beat-based older-onset PD patients ($M = 0.38$, $SE = 0.03$), interval-based older-onset PD patients ($M = 0.34$, $SE = 0.05$), and interval-based young-onset PD patients ($M = 0.34$, $SE = 0.02$). In addition, a 2(sequence: control, test) x 2(age of diagnosis: under 60, 61 and older) mixed measures ANOVA on w values showed neither significant interactions nor main effects (ps > .24). Age of diagnosis was analyzed further by conducting a bivariate Pearson correlation on age of diagnosis and JNDs of the age/disease

groups on the control sequence, showing no significance, $r(19) = -0.05$, $p = .82$. Similarly, Pearson correlations looking at age of diagnosis and *w* values for both the control, $r(19) = 0.17$, $p = .46$, and test sequences, $r(19) = -0.08$, $p = .74$, failed to reach significance.

Another follow-up ANOVA was created to observe whether the class of PD medications that participants took affected beat perception. Many PD patients vary in the types of medications they take to control their motor symptoms, and levodopa-carbidopa or dopamine agonists are often used to treat symptoms. In my sample, patients were taking only levodopa-carbidopa ($n = 8$), a combination of levodopa-carbidopa and dopamine agonists ($n = 8$), or solely dopamine agonists ($n = 5$). I performed a 2 (sequence: control, test) x 2 (listening strategy: interval-based, beat-based) x 3 (medication class: levodopa-carbidopa, levodopa-carbidopa and dopamine agonist, dopamine agonist) x 10 (final time interval: 384 ms, 432 ms, 480 ms, 528 ms, 576 ms, 624 ms, 672 ms, 720 ms, 768 ms, and 816 ms) mixed measures ANOVA on the proportion of "speeding up" responses. Sequence and final time interval were within subject factors, while listening strategy and medication class were between subject factors. No significant four-way interaction was found between sequence, class of PD medications, listening strategy, and final time interval, $F(6.63, 46.43) = 0.60$, $p = .74$. In addition, there was no significant effect for class of PD medications suggesting that the mean proportion of "speeding up" responses did not differ between individuals only taking levodopa-carbidopa, those taking both levodopa-carbidopa and a dopamine agonist, and people taking only dopamine agonists, $F(2, 14) = 0.39$, $p = .68$.

However, the ANOVA revealed a trend towards a three-way interaction between sequence, class of PD medication, and listening strategy, where patients using an interval-based listening strategy and also taking dopamine agonists had lower mean proportion of "speeding up"

response relative to patients taking other drugs and using either a beat-based or interval-based listening strategy, $F(2, 14) = 2.62$, $p = .10$. Patients who used an interval-based listening strategy and were on dopamine agonists had the lowest mean proportion of "speeding up" responses on the test sequence ($M = 0.047$, $SE = 0.01$) relative to patients who recruited an interval-based listening strategy and were on a combination of levodopa-carbidopa and dopamine agonists ($M = 0.19$, $SE = 0.06$), or solely taking levodopa-carbidopa ($M = 0.23$, $SE = 0.05$), as well as patients using a beat-based listening strategy who were solely on dopamine agonists ($M = 0.53$, $SE = 0.07$), a mixture of the two medication types ($M = 0.45$, $SE = 0.48$), or only on levodopa-carbidopa ($M = 0.39$, $SE = 0.06$). I also conducted a 2 (sequence: control, test) x 3 (medication class: levodopa-carbidopa, levodopa-carbidopa and dopamine agonist, dopamine agonist) mixed measures ANOVA on *w* values. No significant interactions or main effects were found between sequence and class of PD medications (*p*s > .32).

Discussion

The aim of this experiment was to test whether the basal ganglia (BG) plays a role in beat perception. To address this issue, I looked at the performance of young adults, older adults, and PD patients on an ambiguous tempo discrimination task to determine whether PD patients were more likely to recruit a different listening strategy relative to controls. Due to dopaminergic denervation of the BG in PD, I hypothesized that PD patients would have weaker beat perception, and use a more interval-based listening strategy, relative to young and older adult controls. Specifically, I predicted that PD patients would have both flatter psychometric curves when looking at the proportion of "speeding up" responses as a function of the final time interval, and have lower *w* values compared to young and older adults.

Contrary to my hypothesis no differences in either the proportion of "speeding up" responses or *w* values were found between young adults, older adults, and PD patients meaning that listening strategy, and consequently, beat perception, did not differ between these groups. However, I did find a difference in discrimination thresholds between PD patients and young adults where PD patients had higher JNDs when compared to young adult controls. Within the PD group, there was a trend towards an interaction where patients using an interval-based listening strategy and solely on dopamine agonists performed the timing task with less accuracy, and had lower mean "speeding up" responses relative to patients on levodopa-carbidopa or a mixture of levodopa-carbidopa and dopamine agonists. Furthermore, another trend suggested that PD patients with a younger age of disease onset performed the task with greater accuracy, having higher mean "speeding up" responses for the 10 final time intervals, in comparison to patients with an older age of disease onset.

My finding that the age/disease groups did not differ on beat perception strength was surprising since previous animal, neuropsychological, pharmacological, and brain imaging studies have posited a strong role for the BG and dopamine in rhythmic temporal processing (Jones & Jahanshahi, 2009; Meck, 2006; Coull et al., 2008; Pouthas et al., 2005; Harrington et al., 2004; Grahn & McAuley, 2009; Grahn & Brett, 2007; Grahn & Brett, 2009; Wiener et al., 2010; Coull et al., 2011; Ferrandez et al., 2003). The initial PD patient data supported the hypothesis of lower *w* values in PD patients relative to controls; however after adding the University of Michigan PD sample, this trend disappeared.

One potential explanation for this unexpected result between the Bowling Green and Michigan patient samples was the range of musical experience. Out of the 14 PD patients tested in Michigan, only two patients had no musical experience, compared to the nine PD patients

without musical experience in the Bowling Green patient sample. However, I did not find a significant correlation between *w* values and years of musical training, which argues against this potential explanation. This finding is supported by Grahn and McAuley (2009) who also found no correlation between *w* values and musical training when administering the same timing task to healthy young adults.

My results do not support previous work suggesting that rhythm perception is impaired in PD patients (Grahn & Brett, 2009). An explanation of these conflicting findings may be that Grahn and Brett had a more complex timing task that required greater cognitive demand from PD patients. Their duration discrimination task required participants to listen to three sequences and judge whether the third sequence was the same or different from the previous two sequences. In contrast, the duration discrimination task I administered only required participants to listen to a single sequence and judge whether the end of the sequence was "speeding up" or "slowing down." This task has been shown to separate strong and weak beat listeners (Grahn & McAuley, 2006; Grahn & McAuley, 2009; Snyder et al., 2011) among healthy young adults, but may not be sensitive to beat perception differences between age/disease groups.

Another potential explanation for my conflicting results may be the difference in demographics of the PD patients I had tested in comparison to the sample tested in the Grahn and Brett (2009) study. Not only did their study test a smaller sample size of PD patients, but they looked at patients across a smaller age range (57 – 80 years) in comparison to my experiment. Thus, the trend in lower *w* values may also potentially disappear with more subjects and a wider variety of young and older PD patients.

I cannot rule out the possibility that there may be compensatory mechanisms from other brain regions involved in beat perception, since besides the BG there has been activation of the

SMA, premotor cortex, superior frontal gyri, and inferior frontal gyrus on duration perception and production tasks (Grahn & Brett, 2007; Grahn & McAuley, 2009). It may be plausible that even without a fully functional BG, some of these cortical areas can execute the neural actions of the BG in beat perception, to an extent. However, this reasoning is unlikely because, if compensatory mechanisms are present for beat perception, there would be no significant difference in beat perception in the Grahn and Brett (2009) study between PD patients and healthy older adults.

I did find a difference between discrimination thresholds between PD patients and healthy young adults, where PD patients had higher JNDs on the control sequence relative to young adult controls. Additionally, the data showed a trend for older adults having higher JNDs when compared to young adults. Because both PD patients and older adults had higher JNDs when compared to young adults, but older adults and PD patients did not differ significantly from each other, this may reflect an age-related impairment, rather than one strictly associated with PD. This finding is consistent with the results of Fitzgibbon and Gordon-Salant (1995), who had found differences in discrimination thresholds by age, where older adults had higher discrimination thresholds when listening to isolated time intervals of tones with varying frequencies, compared to young adults. The study looked at the performance of both older and young adults with and without hearing loss, and found no significant effects of hearing loss. Thus, the PD patients and older adults in my experimental sample may have hearing deficits due to aging, though participants were administered a hearing screening during the testing session.

Interestingly, a trend towards a three-way interaction between sequence, listening strategy, and class of PD medication was found where patients taking dopamine agonists, who also used an interval-based listening strategy had lower mean “speeding up” responses relative to

patients, using an interval- or beat-based approach, taking levodopa-carbidopa or a combination of the therapies, suggesting that medication type can potentially affect temporal perception. Research has shown that PD patients taking dopamine agonists may become more impulsive, or prone to risk-taking behaviors (Claassen et al., 2011; Voon et al., 2011; Weintraub et al., 2006; Weintraub et al., 2010). Weintraub et al. (2010) found that PD patients taking dopamine agonists had a two to three times increased chance in developing impulse control disorders. However, the effect of dopamine agonists on risk-taking behaviors seems to be greater when PD patients are diagnosed with impulse control disorder or show symptoms of it, prior to taking dopamine agonist therapy. Furthermore, impulsivity has shown to affect time perception, specifically, by speeding up the "internal clock." Barratt (1981) studied adolescent psychiatric patients diagnosed as extremely aggressive and adolescent controls on a duration production task. He found that the patients with higher scores on an impulsivity survey under-reproduced time intervals relative to adolescent controls, suggesting that impulsivity can affect an individual's sense of time.

In the current study, PD patients on dopamine agonists may be exhibiting side effects of the medication with an increase in impulsivity resulting in a speeding up of the "internal clock." Consistent with this explanation, even though it did not reach statistical significance, PD patients taking dopamine agonists had lower *w* values for the test sequence, in comparison to patients taking levodopa-carbidopa or a combination of the drug therapies. However, when looking at the proportion of "speeding up" responses as a function of the final time interval, patients categorized in each class of PD medication showed similar S-shaped functions. Since there were no significant interactions between class of PD medication and final time interval, I cannot say with certainty whether PD patients judged most of the sequences as "speeding up" or "slowing

down." A limitation to this analysis was that we did not administer a survey of impulsivity to the PD patients.

Another factor within the PD group was age of diagnosis. I found a trend where patients diagnosed below or at the age of 60, who also recruited a beat-based listening strategy, had higher mean proportion of "speeding up" responses on the test sequence, relative to patients diagnosed older than 60 years who also used a beat-based listening strategy. Moreover, a trend displayed that patients with young-onset PD and a beat-based listening strategy had higher mean proportion of "speeding up" responses in comparison to all patients with older-onset PD as well as young-onset PD patients using an interval-based listening strategy. However, when looking only at patients using an interval-based listening strategy, young- and older-onset PD patients had almost the same mean proportion of "speeding up" responses, suggesting a potential decline with age, in the ability to use a beat-based listening, but not an interval-based listening strategy. Since the ANOVA failed to reveal any significant interactions between age of diagnosis and final time interval, it is difficult to say with certainty how the "speeding up" responses varied with the final variable time intervals, though looking at the proportion of "speeding up" responses as a function of the final time interval, both young- and older-onset PD patients showed similar S-shaped curves. However, as the final time intervals changed to smaller percentage differences which were still less than 600 ms, the older-onset PD curve dropped off more quickly, hinting that more of the older PD patients failed to recognize those final intervals as "speeding up."

A study by Diederich et al. (2003) found that age of disease onset does result in differences in both motor impairment and PD treatment. Individuals with older age of disease onset (78 years of age or older) had significantly higher UPDRS scores, specifically for rigidity, bradykinesia, and axial impairments (which include gait and postural instability) in comparison

to those with younger age of disease onset (43 – 66 years). Older-onset PD patients were also more likely to receive levodopa-carbidopa treatment rather than dopamine agonists. My results suggest a potential perceptual difference associated with age of disease onset that may also show through axial impairments, and support Diederich et al.'s (2003) association between age of disease onset and medication treatment. For instance, the trending difference in average proportion of "speeding up" responses between young- and older-onset PD patients may be associated with the greater motor difficulty older-onset PD patients have in gait, as this has been hypothesized to be a potential rhythmic impairment (Nieuwboer et al., 2001; Thaut et al., 1996). All PD participants scored above 123 on the Dementia Rating Scale-2 so the perceptual difference was not related to a cognitive impairment within the PD group. Supporting Diederich et al. (2003), in the current study, patients diagnosed before or at 60 years of age were taking dopamine agonist therapies, while only one PD patient diagnosed above the age of 60 was taking a combination of dopamine agonists and levodopa-carbidopa therapies.

Research has shown that usually, young-onset PD patients are given dopamine agonists (Diederich et al., 2003; Kostic, 2009) as treatment to delay the usage of levodopa-carbidopa, which is a direct dopamine replacement therapy. The reason for this is that levodopa-carbidopa is associated with motor complications, such as dyskinesia (Antonini, Tolosa, Mizuno, Yamamoto, & Poewe, 2009), and using the medication over a longer period of time results in a shorter duration of effectiveness (also called the "honeymoon effect") where after the first couple of years, the drug has a "wearing off" effect that can last from minutes to hours (Lang & Lozano, 1998b). Furthermore, young-onset PD patients using levodopa-carbidopa as their primary treatment can have an earlier appearance of levodopa-induced dyskinesia (Kostic, 2009). However, most PD patients are put on levodopa therapy eventually, and end up suffering from

PD motor complications at the same rate as PD patients initially taking levodopa-carbidopa (Kostic, 2009). Although dopamine agonists can delay levodopa usage in young-onset PD patients, the results of my study suggest that, beyond side-effects of hypersomnia, hallucinations, and impulse control disorders, there may be effects on beat perception.

Limitations

In addition to the limitations already discussed, this study tested two samples of PD patients from two cohorts within Ohio and Michigan. Sampling from the two recruitment regions may have resulted in different PD treatment by physicians and therapists. Also, few patients with young-onset PD were tested, thus not providing a complete picture of the perceptual abilities of the PD population. PD patients were only tested ON their PD medications, thus potential differences in beat perception between age/disease groups may have been obscured by the replacement of tonic levels of dopamine in the BG through medications. Additionally, specific PD medication dosage information was not obtained from all 21 PD patients; only 14 patients provided us with details of medication dosages, therefore precluding calculation of the levodopa equivalent dosage and its potential effects on beat perception and production. Furthermore, the older adult controls were mostly female, while the PD patients tested in the study were mostly male, so the lack of perceptual differences may have resulted from different distributions of gender in the three age/disease groups. Another limitation was that only PD patients diagnosed before or at 60 years of age were on dopamine agonists, while only one patient over 60 years of age was taking levodopa-carbidopa with a dopamine agonist. Also, the small sample size of PD patients on these medications resulted in a large standard error in the average *w* value of PD patients only on dopamine agonists.

Conclusion and Future Studies

The current findings suggest that although beat perception did not differ between the age/disease groups, there were factors within the PD group, such as class of PD medication and age of diagnosis that might affect beat perception. Though no evidence was found for significant differences in beat perception, follow-up studies should replicate the ambiguous tempo discrimination experiment and observe the performances of a larger PD patient sample, both ON and OFF their anti-parkinsonian medications, from various areas in the U.S.

In the future, it may also be of interest to study beat perception by class of PD medication using a larger sample size of PD participants with more PD patients with an older age of disease onset who are on dopamine agonists, to see if dopamine agonists do speed up the internal clock. Likewise, dosage information should be taken into account to see if the effects of dopamine agonists on beat perception vary by higher or lower medication doses. Furthermore, the interaction between age of diagnosis and PD treatment should be studied, as previous research has shown that PD patients with a younger age of disease onset are more prone to receiving dopamine agonist treatment. It is unknown how young- and older-onset PD patients react to various anti-parkinsonian medications and how these medications might affect their beat perception strengths. Studies should also explore the specific effects of impulsivity on beat perception, by looking at PD patients with impulse control disorders, as approximately 13.6% of PD patients display impulse control disorders (Weintraub et al., 2010). This can greatly affect their lives as it induces gambling, excessive shopping, hypersexuality, and compulsive eating (Weintraub et al., 2010). If dopamine agonist treatment increases the risk of developing impulsivity, physicians should be sensitive to individual differences in clinical symptoms of PD, including impulsiveness, so as not to prescribe PD medications which may exacerbate the current PD symptoms or give rise to new symptoms.

In conclusion, the current study primarily suggests that the BG does not play a major role in beat perception and, perhaps, physicians and physical therapists should have greater sensitivity to individual differences in PD symptoms and clinical factors, to increase the effectiveness of PD treatment through medication and physical rehabilitation.

References

Antonini, A., Moresco, R. M., Gobbo, C., Notaris, R. D., Panzacchi, A., Barone, P.,…Fazio, F. (2002). Striatal dopaminergic denervation in early and late onset Parkinson's disease assessed by pet and the tracer [11C]FECIT: Preliminary findings in one patient with autosomal recessive Parkinsonism. *Neurological Sciences*, *23*, S51-S52.

Antonini, A., Tolosa, E., Mizuno, Y., Yamamoto, M., & Poewe, W. H. (2009). A reassessment of risks and benefits of dopamine agonists in Parkinson. *The Lancet Neurology*, *8*(10), 929-937.

Artieda, J., Pastor, M. A., Lacruz, F., & Obeso, J. A. (1992). Temporal discrimination is abnormal in Parkinson's disease. *Brain*, *115*, 199-210.

Barratt, E. S. (1981). Time perception, cortical evoked potentials and impulsiveness among three groups of adolescents. In J. K. Hays, T. K. Roberts, & K. S. Solway (Eds.), *Violence and the violent individual* (pp. 87-95). New York: Spectrum Publications.

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2007). Basal ganglia, disorders of the motor system. (3rd ed.). *Neuroscience: Exploring the brain*. Philadelphia: Lippincott Williams & Wilkins.

Bonuccelli, U., Del Dotto, P., & Rascol, O. (2009). Role of dopamine receptor agonists in the treatment of early Parkinson’s disease. *Parkinsonism and Related Disorders*, *15S*, S44-S53.

Claassen, D. O., van den Wildenberg, W. P., Ridderinkhof, K. R., Jessup, C. K., Harrison, M. B., Wooten, G. F., & Wylie, S. A. (2011). The risky business of dopamine agonists in

Parkinson disease and impulse control disorders. *Behavioral Neuroscience*, *125*(4), 492-500.

Coull, J. T., Cheng, R., & Meck, W. H. (2011). Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology Reviews*, *36*, 3-25.

Coull, J.T., Nazarian, B., & Vidal, F. (2008). Timing, storage, and comparison of stimulus duration engage discrete anatomical components of a perceptual timing network. *Journal of Cognitive Neuroscience*, 12, 2185-2197.

Davie, C. A. (2008). A review of Parkinson's disease. *British Medical Bulletin*, *86*, 109-127.

de Lau, L. M. L., & Breteler, M. M. B. (2006). Epidemiology of Parkinson's disease. *The Lancet Neurology*, *5*(6), 525-535.

Diederich, N. J., Moore, C. G., Leurgans, S. E., Chmura, T. A., & Goetz, C. G. (2003). Parkinson disease with old-age onset: A comparative study with subjects with middle-age onset. *Archives of Neurology*, *60*, 529-533.

Elsinger, C. L., Rao, S. M., Zimbelman, J. L., Reynolds, N. C., Blindauer, K. A., & Hoffman, R. G. (2003). Neural basis for impaired time reproduction in Parkinson's disease: An fMRI study. *Journal of the International Neuropsychological Society*, *9*, 1088-1098.

Fahn S., Elton R. L, & UPDRS Development Committee. (1987). Unified Parkinson's disease rating scale. In S., Fahn, C.D., Marsden, D.B., Calne, &, M., Goldstein (Eds.), *Recent Developments in Parkinson's Disease* (pp. 153-163). Florham Park, NJ: Macmillan.

Ferrandez, A. M., Hugueville, L., Lehericy, S., Poline, J. B., Marsault, C., & Pouthas, V.

(2003). Basal ganglia and supplementary motor area subtend duration perception: An fMRI study. *Neuroimage*, 19, 1532-1544.

Fitzgibbons, P. J., & Gordon-Salant, S. (1994). Age effects on measures of auditory duration discrimination. *Journal of Speech and Hearing Research, 37*(3), 662-670.

Forno, L. S. (1996). Neuropathology of Parkinson's disease. *Journal of Neuropathology and Experimental Neurology, 55*(3), 259-272.

Freeman, J. S., Cody, F. W. J., & Schady, W. (1993). The influence of external timing cues upon the rhythm of voluntary movements in Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry, 56*(10), 1078-1084.

Goberman, A., Elmer, L., Mackowiak, E., & Heaton, B. (2004). Parkinsonian speech variability: Medication-related fluctuations across 3 days. Presented at the *12th Biennial Conference on Motor Speech: Motor Speech Disorders and Speech Motor Control*. Albuquerque, NM.

Grahn, J. A., & Brett, M. (2007). Rhythm and beat perception in motor areas of the brain. *Journal of Cognitive Neuroscience, 19*(5), 893-906.

Grahn, J. A., & Brett, M. (2009). Impairment of beat-based rhythm discrimination in Parkinson's disease. *Cortex, 45*(1), 54-61.

Grahn, J. A., & McAuley, J. D. (2009). Neural bases of individual differences in beat perception. *Neuroimage, 47*(4), 1894-1903.

Grahn, J. A., & Rowe, J. B. (2006). Feeling the beat: Premotor and striatal interactions in musicians and non-musicians during beat perception. *The Journal of Neuroscience, 29*(23), 7540-7548.

Grondin, S. (2010). Timing and time perception: A review of recent behavioral and neuroscience findings and theoretical directions. *Attention, Perception, & Psychophysics, 72*(3), 561-582.

Harel, B. T., Cannizzaro, M. S., Cohen, H., Reilly, N., & Snyder, P. J. (2004). Acoustic characteristics of Parkinsonian speech: A potential biomarker of early disease progression and treatment. *Journal of Neurolinguistics, 17*(6), 439-453.

Harrington, D. L., Boyd, L. A., Mayer, A. R., Sheltraw, D. M., Lee, R. R., Huang, M., & Rao, S. M. (2004). Neural representation of interval encoding and decision making. *Cognitive Brain Research,* 21, 193-205.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression, and mortality. *Neurology*, *17*, 427-442.

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, *4*(2), 97-110.

Hornykiewicz, O. (1998). Biochemical aspects of Parkinson's disease. *Neurology*, *51*, S1-S9.

Jahanshahi, M., Jenkins, I. H., Brown, R. G., Marsden, C. D., Passingham, R. E., Brooks, & D. J. (1995). Self-initiated versus externally triggered movements: An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain*, *118*(4), 913-933.

Jankovic, J. (2007). Parkinson's disease: Clinical features and diagnosis. *Journal of Neurology, Neurosurgery, and Psychiatry with Practical Neurology*, *79*, 368-376.

Jankovic, J., McDermott, M., Carter, J., Gauthier, S., Goetz, C., Golbe, L.,…Parkinson Study Group. (1990). Variable expression of Parkinson's disease: A base-line analysis of the DATATOP cohort. *Neurology, 40*(10), 1529-1534.

Jones, C. & Jahanshahi, M. (2009). The substantia nigra, the basal ganglia, dopamine and temporal processing. *Journal of Neural Transmission,* 73:161-171.

Jurica, P. J., Leitten, C. L., & Mattis, S. (2001). *Dementia rating scale-2: Professional manual*. Psychological Assessment Resources.

Kegl, J., Cohen, H., & Poizner, H. (1999). Articulatory consequences of Parkinson's disease: Perspectives from two modalities. *Brain and Cognition, 40*(2), 355-386.

Lang, A. E., & Lozano, A. M. (1998a). Parkinson's disease: First of two parts. *The New England Journal of Medicine, 339*(15), 1044-1053.

Lang, A. E., & Lozano, A. M. (1998b). Parkinson's disease: Second of two parts. *The New England Journal of Medicine, 339*(16), 1130-1143.

Lewis, S. J., Foltynie, T., Blackwell, A. D., Robbins, T. W., Owen, A. M., & Barker, R. A. (2005). Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(3), 343-348.

Macar, F., Lejeune, H., Bonnet, M., Ferrara, A., Pouthas, V., Vidal, F., & Maquet, P. (2002). Activation of the supplementary motor area and of attentional networks during temporal processing. *Experimental Brain Research,* 142, 475-485.

Macmillan, N. A., Creelman, C. D., 1991. *Detection theory: A user's guide.* New York: Cambridge University Press.

McAuley, J. D., Frater, D., Janke, K., & Miller, N. (2006). Detecting changes in timing: Evidence for two modes of listening. Paper presented at *9th International*

Conference on Music Perception and Cognition. University of Bologna. Retrieved from http://www.marcocosta.it/icmpc2006/pdfs/52.pdf

McAuley, J. D., & Jones, M. R. (2003). Modeling effects of rhythmic context on perceived duration: A comparison of interval and entrainment approaches to short-interval timing. *Journal of Experimental Psychology: Human Perception and Performance, 29*(6), 1102-1125.

Meck, W. H. (1996). Neuropharmacology of timing and time perception. *Cognitive Brain Research, 3*, 227-242.

Meck, W. H. (2006). Neuroanatomical localization of an internal clock: A functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. *Brain Research, 1109*(1), 93-107.

Meireles, J., & Massano, J. (2012). Cognitive impairment and dementia in Parkinson's disease: Clinical features, diagnosis, and management. *Frontiers in Neurology, 3*, 1-15.

Merchant, H., Luciana, M., Hooper, C., Majestic, S., & Tuite, P. (2008). Interval timing and Parkinson's disease: Heterogeneity in temporal performance. *Experimental Brain Research, 184*(2), 233-248.

Morris, M. E. (2000). Movement disorders in people with Parkinson disease: A model for physical therapy. *Physical Therapy, 80*, 578-597.

Nieuwboer, A., Dom, R., De Weerdt, W., Desloovere, K., Fieuws, S., & Broens-Kaucsik, E. (2001). Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. *Movement Disorders, 16*(6), 1066-1075.

O’Boyle, D. J., Freeman, J. S., & Cody, F. W. J. (1996). The accuracy and precision of

timing of self-paced, repetitive movements in subjects with Parkinson's disease. *Brain, 119,* 51-70.

Pouthas, V., George, N., Poline, J. B., Pfeuty, M., Vandemoorteel, P. F., Hugueville, L., Ferrandez, A. M., Lehericy, S., Lebihan, D., Renault, B. (2005). Neural network involved in time perception: An fMRI study comparing long and short interval estimation. *Human Brain Mapping,* 25, 433-441.

Pastor, M. A., Artieda , J., Jahanshahi, M., & Obeso, J. A. (1992). Time estimation and production is abnormal in Parkinson's disease. *Brain*, *115,* 211-225.

Radloff, L. R. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385-401.

Rascol, O., Payoux, P., Ory, F., Ferreira, J. J., Brefel-Courbon, C., & Montastruc, J. L. (2003). Limitations of current Parkinson's disease therapy. *Annual Neurology, 53,* S3-S15.

Risen, J. M., & Schnider, A. (2001). Time estimation in Parkinson's disease: Normal long duration estimation despite impaired short duration discrimination. *Journal of Neurology*, *248*, 27-35.

Schwartze, M., Keller, P. E., Patel, A. D., & Kotz, S. A. (2011). The impact of BG lesions on sensorimotor synchronization, spontaneous motor tempo, and the detection of tempo changes. *Behavioral Brain Research,* 685-691.

Skodda, S., & Schlegel, U. (2008). Speech rate and rhythm in Parkinson's disease. *Movement Disorders, 23*(7), 985-992.

Snyder, J. S., Pasinski, A. C., & McAuley, J. D. (2011). Listening strategy for auditory rhythms modulates neural correlates of expectancy and cognitive processing. *Psychophysiology*, *48*, 198-207.

Spencer, R. M. C., & Ivry, R. B. (2005). Comparison of patients with Parkinson's disease or cerebellar lesions in the production of periodic movements involving event-based or emergent timing. *Brain and Cognition, 58,* 84-93.

Thaut, M. H., McIntosh, G. C., Rice, R. R., Miller, R. A., Rathbun, J., & Brault, J. M. (1996). Rhythmic auditory stimulation in gait training for Parkinson's disease patients. *Movement Disorders, 11*(2), 193-200.

Thaut, M. H., McIntosh, K. W., McIntosh, G. C., & Hoemberg, V. (2001). Auditory rhythmicity enhances movement and speech motor control in patients with Parkinson's disease. *Functional Neurology, 16*(2), 163-172.

Todd, R., Boltz, M., & Jones, M. R. (1989). The MIDILAB auditory research system. *Psychomusicology,* 8, 17-30.

Tomlinson, C. L., Stowe, R., Patel, S., Rick, C., Gray, R., & Clarke, C. E. (2010). Systematic review of levodopa equivalency reporting in Parkinson's disease. *Movement Disorders*, *25*(15), 2649-2685.

Voon, V., Gao, J., Brezing, C., Symmonds, M., Ekanayake, V., Fernandez, H.,…Hallett, M. (2011). Dopamine agonists and risk: Impulse control disorders in Parkinson's disease. *Brain*, *134*, 1438-1446.

Weintraub, D., Siderowf, A. D., Potenza, M. N., Goveas, J., Morales, K. H., Duda, J. E.,…Stern, M. B. (2006). Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Archives of Neurology, 63*(7), 969-973.

Weintraub, D., Koester, J., Potenza, M. N., Siderowf, A. D., Stacy, M., Voon, V., & Lang, A. E. (2010). Impulse control disorders in Parkinson disease: A cross-sectional study of 3090 patients. *Archives of Neurology, 67*(5), 589-595.

Wiener, M., Turkeltaub, P., & Coslett, H. B. (2010). The image of time: A voxel-wise meta-analysis. *NeuroImage, 49,* 1728-1740. DOI: 10.1016/j.neuroimage.2009 .09.064

Zetusky, W. J., Jankovic, J., & Pirozzolo, F. J. (1985). The heterogeneity of Parkinson's disease: Clinical and prognostic implications. *Neurology, 35*(522), 526.

Footnotes

[1]Since each age/disease group had a different range of *w* values, I performed a median split on *w* values to accurately assess if each individual was more of an interval- or beat-based listener relative to other individuals in their age/disease group. Young adults (n = 14), were split on a *w* value of 0.81, older adults (n = 19) were split on a *w* value of 0.66, and PD patients (n = 21) were split on a *w* value of 0.80. Beat-based listeners had *w* values above and interval-based listeners had *w* values below the respective median values. Participants who fell on the median value were placed in the interval-based listener group.

Acknowledgments

Sariha Ima Moyen, Department of Psychology, University of Michigan, Ann Arbor.

First off, I must thank Dr. Rachael Seidler, my mentor and primary investigator, as well as Dr. Nathaniel Miller, my secondary mentor and collaborator on the project. They have provided continuous guidance, patience, and the utmost sincerity in helping me complete this research; I am grateful for the knowledge I've gained on how to conduct independent research from this wonderful group of faculty members. Additional thanks to Lauren Curley, who became my "unofficial" mentor with her tech-savvy skills. I would also like to thank all of the members of the Neuromotor Behavior lab at the University of Michigan for their valuable suggestions and criticisms on the project. Thank you especially to my parents, Farhana Moyen and Munshi Moyenuddin, as well as my brothers, Saajid and Sayeef, who have been my constant blanket of support and encouragement through this entire process.

Table 1

PD Patient Characteristics

Participant	Age	Sex	Years Diagnosed	DRS-2	Education (years)	UPDRS	Years of Musical Training	DA-Enhancing Medication(s)	LED* (mg)
1	60	M	3.5	143	16	10	3	5, 8, 11	---
2	62	M	1.5	138	16	8	0	5, 6, 7	---
3	67	M	3	140	12	19	0	1, 3, 7	---
4	64	M	4	139	16	18	0	4, 6, 12	---
5	61	M	10	137	12	18	0	1, 5, 6	---
6	70	F	10	142	12	7	0	5, 6, 8	---
7	77	M	13	126	16	36	4	1, 3	---
8	66	M	3	142	16	14	0	1, 3, 6	---
11	40	F	4	142	13	10	0	1, 3, 6	---
12	60	M	3	140	16	17	50	1, 3, 5, 6, 7, 9	---
13	76	F	7	138	18	18	0	1	---
14	57	F	9	135	12	22	5	10	450
15	63	M	10	138	19	12	0	1, 5, 6, 8	280.5
17	65	F	5	141	16	22	13	1, 10	901.5
18	63	M	5	136	16	29	7	1, 6, 7	120
19	69	M	16	143	22	29	4.25	3, 11	100.375
21	66	M	12	141	16	33	5	2	264
23	83	M	8	140	16	32	2	1	1.5
25	73	M	11	143	23	29	17	1, 10	202.25
26	69	M	5	142	17	15	21	1	0.5
27	53	M	7	132	14	32	0	1	0.5
Mean	**64.95**		**7.14**	**138.95**	**15.90**	**20.48**	**6.25**		**218.99**
SD	**9.04**		**3.94**	**4.15**	**2.96**	**9.0**	**11.67**		**278.34**

Note. Participant characteristics for the 21 PD patients whose data were used in the study; the six patients whose data analyses were excluded are not shown in this table. SD = standard deviation; DRS-2 = Dementia Rating Scale (2nd edition); UPDRS-Motor = Unified Parkinson's Disease Rating Scale-motor examination; LED = Levodopa Equivalence Dose, measure of PD medications standardized to the effect of 100 mg of levodopa (Tomlinson et al., 2010). *Medication dosage was not collected for participants 1-13. 1 = levodopa-carbidopa (regular); 2 = levodopa-carbidopa and entacapone (Stalevo); 3 = levodopa-carbidopa controlled release (CR); 4 = ropinirole (Requip); 5 = ropinirole-extended release (Requip XL); 6 = rasagiline (Azilect); 7 = clonazepam; 8 = amantadine; 9 = entacapone (Comtan); 10 = pramipexole dihydrochloride (Mirapex); 11 = selegiline; 12 = profenamine hydrochloride (Parsitan).

Table 2
Older Adult Characteristics

Participant	Age	Sex	DRS-2	Years of Musical Training
1	54	M	---	0
2	60	F	---	0
3	56	F	---	9
5	68	F	---	3
7	63	F	---	16
9	87	F	---	3
10	67	F	141	50
11	69	M	139	3
12	57	F	142	19
14	69	F	138	1.08
15	74	F	144	7
16	62	F	141	0
17	60	F	138	7
18	60	F	143	72
19	61	F	143	2
20	78	F	142	.75
23	58	M	142	0
24	58	F	141	1
25	79	F	133	3
Mean	**65.26**		**140.54**	**10.36**
SD	**8.95**		**2.93**	**18.98**

Note. Participant characteristics for the 19 older adults whose data were used in the study; the four participants whose data analyses were excluded are not shown in this table. SD = standard deviation; DRS-2 = Dementia Rating Scale (2nd edition), *The DRS-2 was not administered to older adult participants 1-9.

Table 3
Young Adult Characteristics

Participant	Age	Sex	Years of Musical Training
2	21	F	0
3	20	F	0
4	28	M	0
5	24	F	7
6	28	M	.08
8	21	F	8.50
9	18	F	0
11	21	M	0
14	29	F	7
18	21	M	0
19	20	M	0
20	27	F	0
21	19	M	2
22	22	M	7
Mean	**22.79**		**2.26**
SD	**3.70**		**3.42**

Note. Participant characteristics for the 14 young adults whose data were used in the study; the one participant whose data analysis was excluded is not shown in this table. SD = standard deviation.

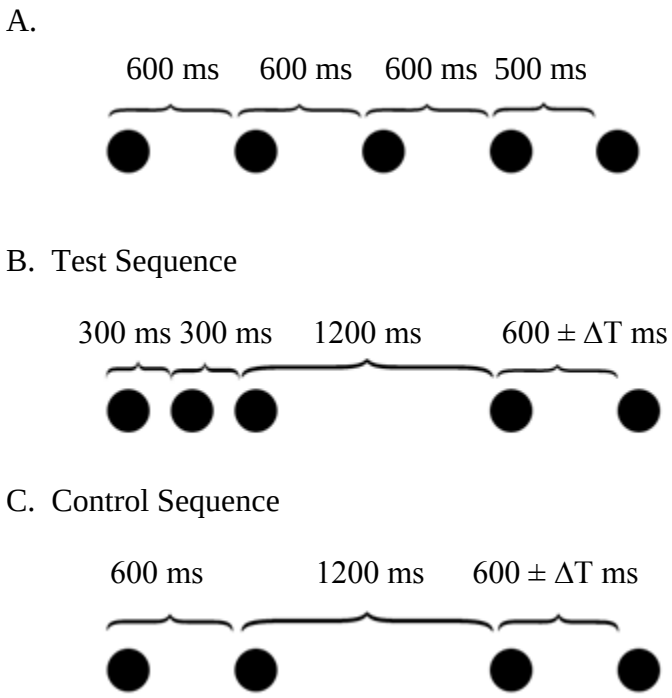

Figure 1. Schematic of three tone sequences. A. An equally-timed (isochronous) sequence of three 600 ms time intervals and a final 500 ms (shortened) time interval. This sequence is included for reference; this sequence was not presented to participants. B. The test sequence was delineated by two 300 ms time intervals followed by a 1200 ms time interval, and a final variable time interval centered on 600 ms. C. The control sequence was delineated by a 600 ms time interval, a 1200 ms time interval, and a variable final interval centered on 600 ms. Participants judged whether the end of each sequence, both control and test, was “speeding up” or “slowing down.”

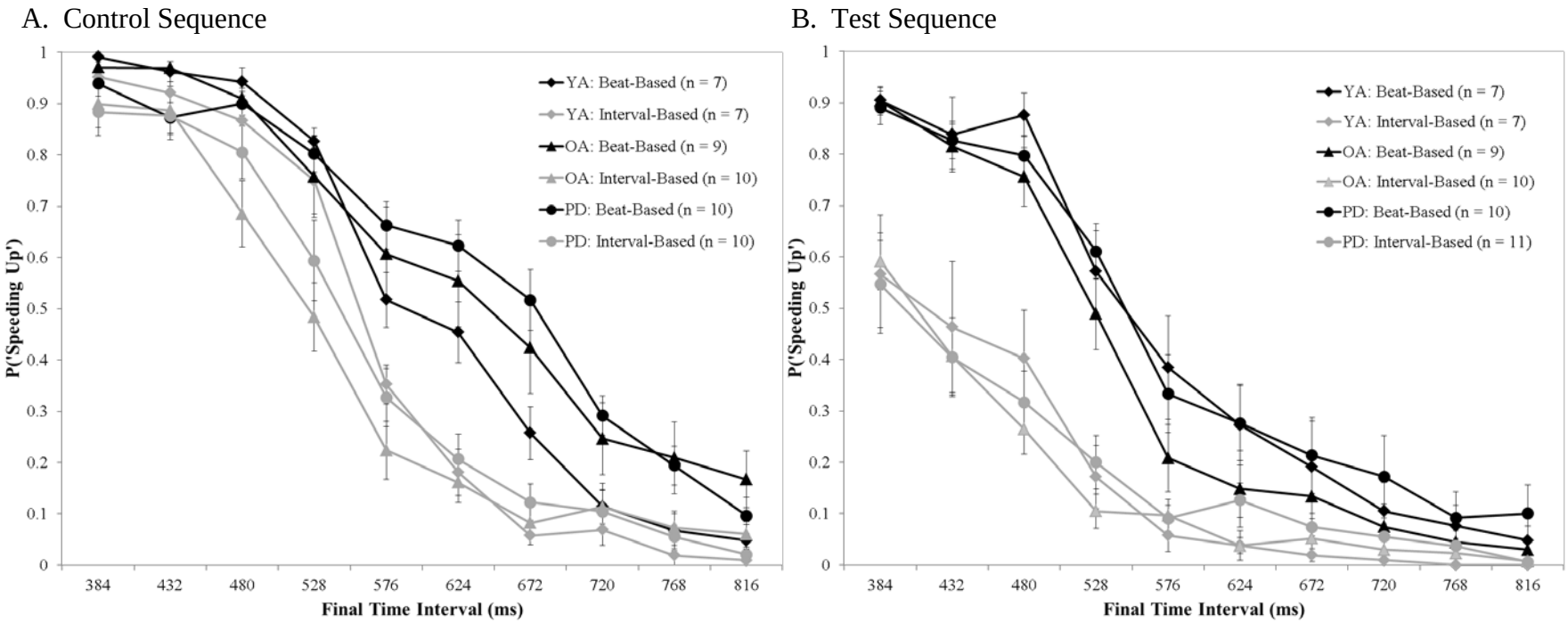

Figure 2. The mean proportion of "speeding up" responses as a function of listening strategy and age/disease group for the 10 final time intervals. Listening strategy was determined by performing a median split on *w* values within each age/disease group. Individuals with *w* values above the median were labeled as "beat-based" listeners, and those with *w* values equal to or below the median were labeled as "interval-based" listeners. A. Young adults (YA), older adult controls (OA) and PD patients had a similar pattern of "speeding up" responses for the control sequence; however, the proportion of "speeding up" responses varied between interval and beat-based listeners from 552 ms to 696 ms. B. No differences were found in the proportion of "speeding up" responses between the age/disease groups and the proportion of participants that fell into the two listening strategies were relatively equal.

However, paralleling previous studies, differences in the pattern of “speeding up” responses differed between beat- and interval-based listeners. Beat-based listeners have a S-shaped curve, suggesting that they judge the test sequence to be “speeding up” when the final interval is less than 600 ms, and “slowing down” when the final interval is greater than 600 ms. Interval-based listeners show more curvilinear pattern of responses, suggesting that they tended to judge the test sequence as “slowing down” more often.

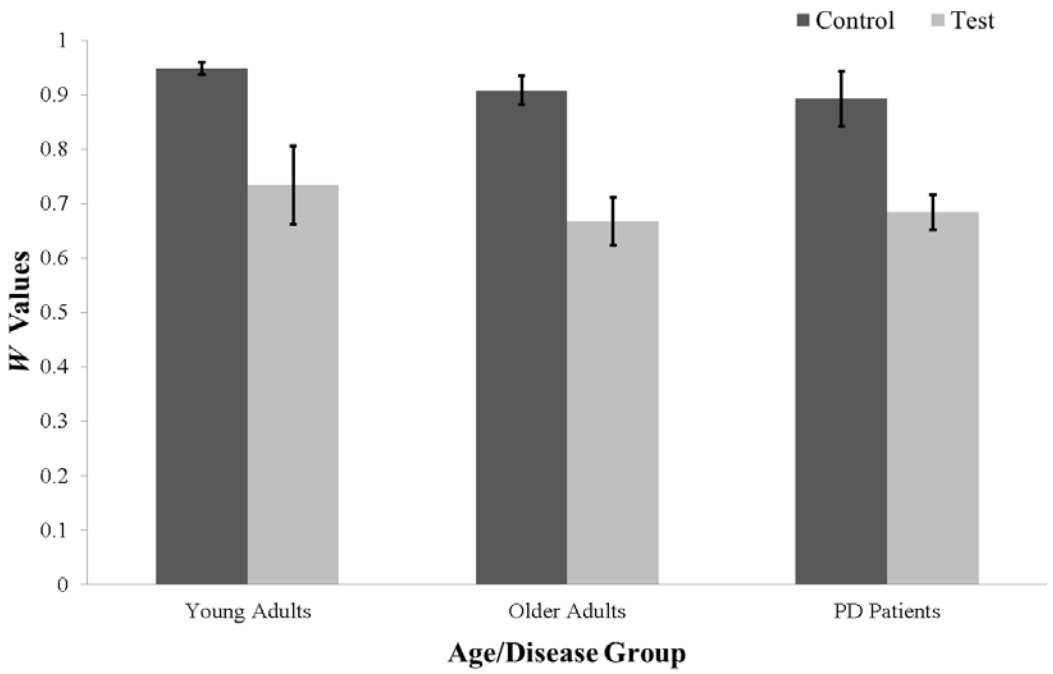

Figure 3. Mean *w* values as a function of age/disease group and sequence. *W* values are bound between 0-1, with values closer to 0 suggesting the use of an interval-based listening strategy and values closer to 1 indicating a beat-based listening strategy. Similar *w* values were found for both the control and test sequences between the age/disease groups.

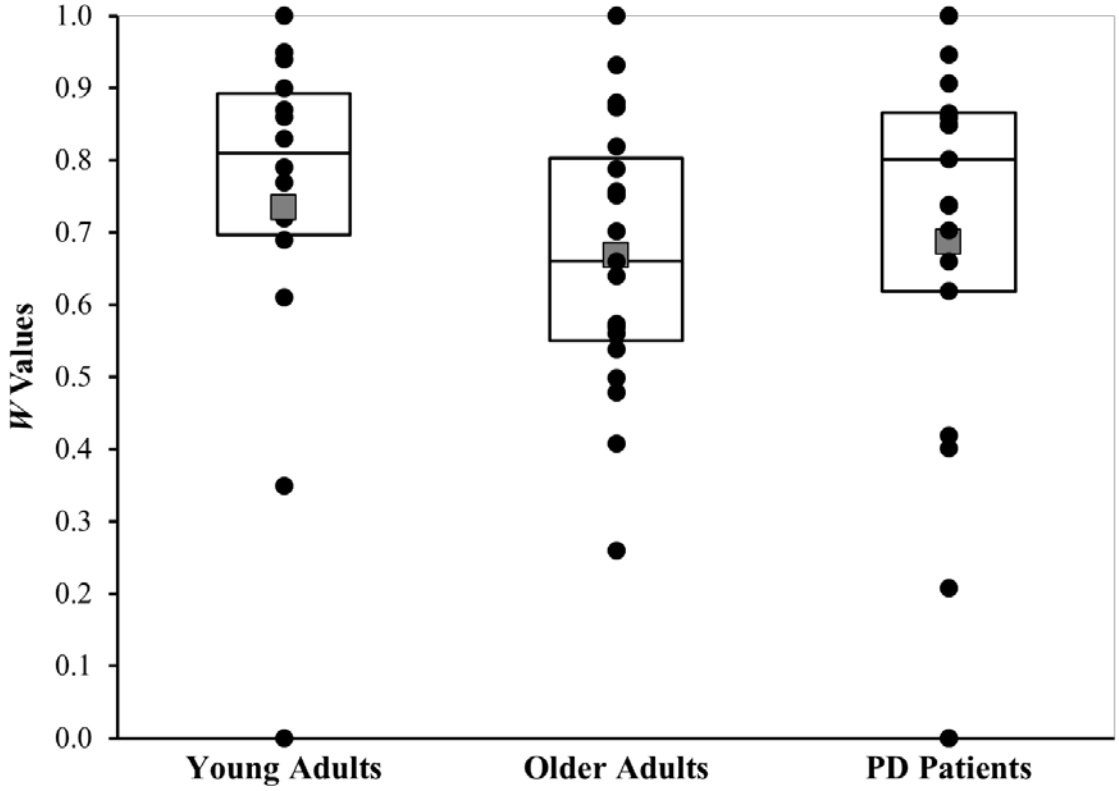

Figure 4. Boxplot showing each participant's *w* value as a function of age/disease group for the test sequences. The dark grey squares within each box shows the group mean. Older adults and PD patients show a wider distribution of *w* values, relative to young adults. However, all three age/disease groups cluster toward *w* values closer to 1. This implies there are not large differences between age/disease groups in *w* values, and that group averages in *w* values are fairly representative of the data.